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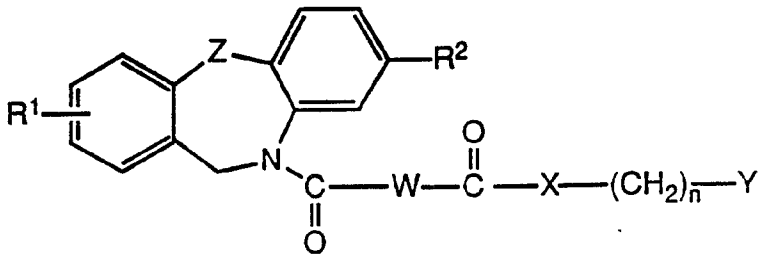
(54) Title: 10-ACYL-DIBENZ(B,F) (1,4)-OXAZEPINES AND THEIR THIAZEPINES ANALO GUES USEFUL AS PROSTAGLANDIN ANTAGONISTS



(I)

(57) Abstract

The present invention provides substituted dibenzoxazepine compounds of formula (I), which are useful as analgesic agents for the treatment of pain, pharmaceutical compositions comprising a therapeutically-effective amount of a compound of formula (I) in combination with a pharmaceutically-acceptable carrier, and a method for eliminating or ameliorating pain in an animal comprising administering a therapeutically-effective amount of a compound of formula (I) to the animal.

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10-ACYL-DIBENZ(B,F)(1,4)-OXAZEPINES AND THEIR THIAZEPINES ANALOGUES USEFUL AS PROSTAGLANDIN ANTAGONISTS

BACKGROUND OF THE INVENTION

(1) Field of the Invention

The present invention generally relates to compounds having pharmacological activity which are useful as pharmacological agents and, more particularly, as analgesic agents for the treatment of pain, to pharmaceutical compositions containing one or more of these compounds, and to methods of treatment employing these compounds. More particularly, the present invention concerns substituted dibenzoxazepine compounds, pharmaceutical compositions containing one or more of these compounds in combination with a pharmaceutically-acceptable carrier, and methods of treating pain employing these compounds.

Analgesic compounds are agents which alleviate pain without causing a loss of consciousness and, thus, which are useful for treating pain and, often, for reducing inflammation.

The major classes of analgesic compounds include narcotic analgesics, or opiates, compounds which alleviate pain and induce sleep, and analgesic-antipyretic compounds, compounds which alleviate pain and reduce fever, such as salicylates.

Although the efficacy of opiates in relieving pain is well established, the associated addiction liability of opiates is a distinct disadvantage of these compounds.

While salicylate and salicylate-like agents (non-steroidal antiinflammatory agents or NSAIDS) are also efficacious in relieving pain, they often exhibit undesirable side effects, such as gastrointestinal irritation, as with aspirin, allergic response, as with aspirin, and/or liver toxicity with extended use, as with acetaminophen.

The compounds of the present invention are neither opiates nor salicylates, and represent another class of compounds which are useful as analgesic agents.

(2) Description of the Related Art

U.S. Patent Nos. 4,559,336 and 4,614,617 (a continuation-in-part of U.S. 4,559,336) disclose 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-(sulfinyl- and sulfonyl-containing acyl)hydrazides, and intermediates thereof.

U.S. Patent No. 3,534,019 discloses hydrazides of dibenzoxazepine-, dibenzothiazepine- and dibenzodiazepine-carboxylic acids.

U.S. Patent No. 3,624,104 discloses aralkanoyl derivatives of dibenzoxazepine-N-carboxylic acid hydrazide compounds.

U.S. Patent No. 3,989,719 discloses N,N'-diacyl hydrazines.

U.S. Patents Nos. 3,917,649 and 3,992,375 (a divisional of U.S. Patent No. 3,917,649) disclose dibenzoxazepine N-carboxylic acid hydrazine compounds.

U.S. Patents Nos. 4,045,442, 4,125,532 (a divisional of U.S. Patent No. 4,045,442) and 4,170,593 (a divisional of U.S. Patent No. 4,125,532) disclose 1-(substituted amino)alkanoyl-2-(dibenzoxazepine-10-carbonyl)hydrazine compounds.

U.S. Patent No. 4,559,337 discloses 8-chlorodibenz-[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-(alkoxy-containing acyl)hydrazide compounds.

GB 1 522 003 discloses 1-acyl-2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine-10-carbonyl)hydrazine compounds.

GB 1 331 892 discloses derivatives of dibenzoxazepine N-carboxylic acid hydrazides.

European Patent Application Publication No. 0 193 822 discloses 8-chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carboxylic acid, 2-(thio-, sulfinyl- and sulfonyl-containing acyl)hydrazide compounds.

European Patent Application Publication No. 0 218 077 discloses 8-chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carboxylic acid, 2-[(substituted phenylsulfinyl)alkanoyl]hydrazide compounds and 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[(substituted phenylsulfonyl)alkanoyl]hydrazide compounds, and intermediates used in the preparation of these compounds.

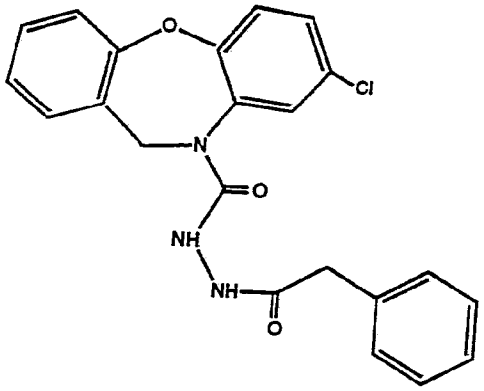
European Patent Application Publication No. 0 012 385 discloses dibenz[b,f][1,4]oxazepine-derivatives.

German Patent Application Publication No. 1,170,322 discloses 10-substituted-dibenz-[b,f][1,4]oxazepin-11(10H)-ones.

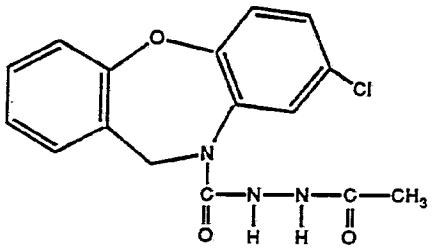
Netherlands Patent No. 67,00603 discloses substituted dibenz[b,f][1,4]oxazepine-11(10H)-one compounds.

Drower et al., "The Antiociceptive Effects of Prostaglandin Antagonists in the Rat," *European Journal of Pharmacology, 133*, 249-256 (**1987**), disclose the study of the antinociceptive properties of two competitive antagonists of prostaglandins of the E series, 8-chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carboxylic acid, 2-acetylhydrazide and 8-chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carboxylic acid, 2-(5-chloro-1-oxopentyl)hydrazide.

J. H. Sanner, "Dibenzoxazepine Hydrazides as Prostaglandin Antagonists," *Intra-Science Chem. Rept.*, *6*(1), 1-9 (**1972**), describes experiments performed with two dibenzoxazepine derivatives designated SC-18637 and SC-19220, and shown below, and found that SC-18637 and SC-19220 inhibit the stimulant actions of prostaglandins on isolated smooth muscle preparations.



SC-18637



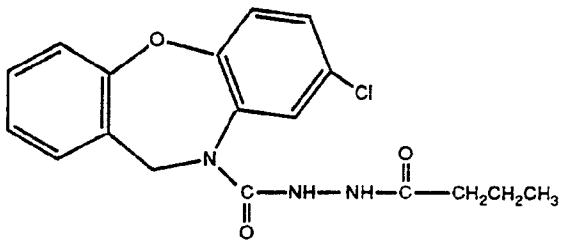
SC-19220

K. Nagarajan et al., "Synthesis of 10,11-Dihydrodibenz[b,f][1,4]oxazepine Derivatives as Potential Anticonvulsants & Psychotropic Agents," *Indian Journal of Chemistry, 24B*, 840-844 (**1985**), disclose the synthesis of acyl, carbamoyl and thiocarbamoyl derivatives of 10,11-dihydrodibenz-[b,f][1,4]oxazepine, most of which have either a nitro or an amino group at position-2, as analogues of carbamazepine, and the evaluation of these derivatives as anticonvulsants associated with neuroleptic activity.

Other art which relates to the present invention includes that which is discussed below.

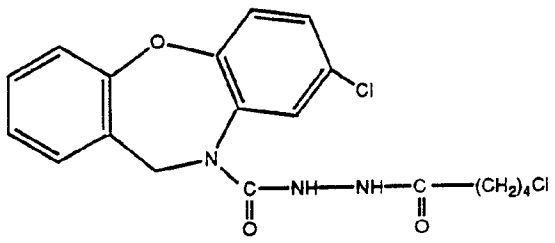
D.E. MacIntyre et al., "Antagonism of Human Platelet Responses to Stimulatory and Inhibitory Prostaglandins," *Prog. Lipid. Res.*, *20*(1-4), 453-9 (**1981**), disclose on Page 454, Lines 11-12, Page 458, Lines 43-44, and in Table 1, two dibenzoxazepine compounds designated SC-19220 and SC-25191, and shown

above and below, respectively, which were employed in an investigation of the effects of prostaglandin antagonists on platelet responses to stimulatory and inhibitory prostaglandins.



SC-25191

R. Gimet et al., "Quantitative Determination of Polymorphic Forms in a Formulation Matrix Using the Near Infra-Red Reflectance Analysis Technique," *J. Pharmaceutical & Biomedical Analysis*, 5(3), 205-211 (**1987**), disclose an analytical method for the determination of the polymorphic transformation of an active ingredient in a solid dosage form matrix, and discuss a compound designated SC-25469, and shown below, at Page 206, Lines 16-23.



SC-25469

J.H. Sanner et al., "Structure-Activity Relationships of some Dibenzoxazepine Derivatives as Prostaglandin Antagonists," *Advances in the Biosciences*, *9*, 139-148 (**1972**), disclose tests for prostaglandin antagonism on isolated guinea-pig ileum

and rat stomach fundus strips with the n-butanoyl, i-butanoyl and n-hexanoyl analogs of SC-19220 and, on Page 140, Lines 11-18, show the chemical structures of the compounds used in the study.

A. Rakovska et al., "Antagonistic Effect of SC-19220 on the Responses of Guinea-Pig Gastric Muscles to Prostaglandins E_1, E_2 and F_2," *Arch. int. Pharmacodyn*, *268*, 59-69 (**1984**), disclose a study of the contractile responses of guinea-pig gastric muscles to SC-19220, and the prostaglandin-blocking activity and specificity of SC-19220 on these muscles.

W. E. Coyne et al., "Anticonvulsant Semicarbazides," *J. Med. Chem.*, *11*(6), 1158-1160 (**1968**), disclose the investigation of the structure-activity relationship of the anticonvulsant activity of a series of semicarbazides which was synthesized from various tricyclic amines (see Table I, Page 1160).

K. Gyires et al., "The Use of the Writhing Test in Mice for Screening Different Types of Analgesics," *Arch. int. Pharmacodyn*, *267*, 131-140 (**1984**), describe a comparison of the analgesic potency of some prostaglandin synthesis inhibitors, including SC-19220, and morphine using the writhing test. SC-19220 is discussed on Page 133, Lines 10 and 14-16, in Table II (Page 134), and on Page 135, Lines 16-25, and Page 137, Lines 34-38.

A. Bennett et al., "Antagonism of Prostanoid-Induced Contractions of Rat Gastric Fundus Muscle by SC-19220, Sodium Meclofenamate, Indomethacin or Trimethoquinol," *Br. J. Pharmac*, *71*, 169-175 (**1980**), disclose the study of the effects of several compounds, including SC-19220, on contractions of the rat stomach longitudinal muscle to several prostanoids. SC-19220 is discussed on Page 175, Paragraph 1, Page 170, Paragraph 4, in Table 1 and Figure 2, on Page 172, Paragraph 2, and on Page 174, Paragraphs 1 and 2.

C. A. Maggi et al., "The Effect of SC-19220, a Prostaglandin Antagonist, on the Micturition Reflex in Rats," *European Journal of Pharmacology, 152,* 273-279 **(1988)**, disclose a study in which SC-19220 is said to have increased the bladder capacity and reduced the voiding efficiency of micturition of urethane-anesthetized rats.

George et al., "Antagonism of Alcohol Hypnosis by Blockade of Prostaglandin Synthesis and Activity: Genotype and Time Course Effects," *Pharmacology Biochemistry & Behavior, 19,* 131-136 **(1983)**, disclose a study of genetic and time-course factors of the effect of the antagonism of alcohol-induced behaviors of mice which have been pretreated with prostaglandin synthetase inhibitors and the effect of SC-19220 on ethanol sleep time.

S. Nakajyo et al., "Inhibitory Effect of Bassianolide, A Cyclodepsipeptide, on Drug-Induced Contractions of Isolates Smooth Muscle Preparations," *Japan. J. Pharmacol., 32,* 55-64 **(1982)**, disclose a study of the effect of bassianolide on the contractile responses induced by various types of neurotransmitters and autacoids. SC-19220 was employed in this study, and is discussed on Page 57, Paragraph 1, in Figures 2 and 3, in Table 1, and on Page 60, Paragraph 1, Page 62, Paragraph 3, and Page 63, Paragraph 2.

A. Gomes et al., "Pharmacodynamics of Venom of the Centipede Scolopendra subspinipes dehaani," *Indian Journal of Experimental Biology, 20,* 615-618 **(1982)**, disclose an investigation of the pharmacodynamic actions of the venom of the tropical centipede S. subspinipes. SC-19220 was employed in this study and is discussed on Page 615 (abstract), Page 616, Line 30, Page 617, Lines 13-18, in Figures 4 and 5, and on Page 618, Lines 23-26.

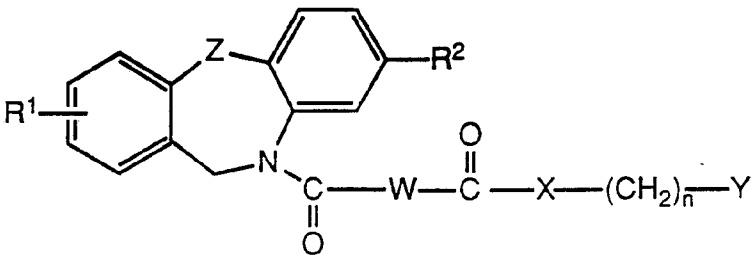
Each of the documents described hereinabove discloses compounds which are structurally different from the compounds of the present invention. Thus, the compounds of the present invention are structurally distinct from that which has been described in the art.

Compounds of the present invention have been found to exhibit activity as prostaglandin E_2 antagonists. Some of these compounds were surprisingly and unexpectedly found to be equipotent as prostaglandin E_2 antagonists compared to prostaglandin antagonists reported in the literature, which are structurally different from the compounds of the present invention.

Moreover, compounds within the present invention, such as the compound shown and described in Example 8 hereinbelow, were found to be highly water soluble. Thus, these compounds may be much more easily formulated into compositions which are suitable for oral, parenteral and other modes of administration than compounds which are not water soluble.

SUMMARY OF THE INVENTION

The present invention provides compounds having a structure of Formula I:



Formula I

or a pharmaceutically-acceptable salt, ester or amide thereof, wherein:

R^1 is hydrogen, halogen, hydroxy or $-O-\overset{O}{\overset{\|}{C}}-R^3$;

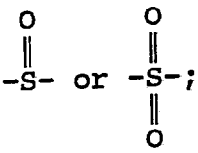
R^2 is hydrogen, halogen or trifluoromethyl;

R^3 is hydrogen or alkyl;

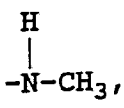
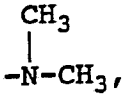
W is $-CH=CH-$, $-(CH_2)_2-$ or $-C\equiv C-$;

X is oxygen or -NH-;

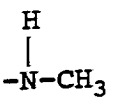
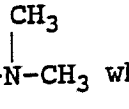
n is an integer of from 0 to 5;

Z is oxygen, sulfur,  or ;

Y is hydrogen, alkyl, hydroxy, alkoxy, aryl,

heteroaryl, $-NH_2$,  , or  ,

with the proviso that Y is not hydroxy, alkoxy,

$-NH_2$,  or  when n is 0.

The present invention also provides pharmaceutical compositions which are pharmaceutically acceptable, and which comprise a therapeutically-effective amount of a compound of Formula I in combination with a pharmaceutically-acceptable carrier, and a method for eliminating or ameliorating pain in an animal comprising administering a therapeutically-effective amount of a compound of Formula I to the animal.

DETAILED DESCRIPTION OF THE INVENTION

(1) Definitions

For purposes of clarity, the terms and phrases used throughout this specification and the appended claims are defined in the manner set forth directly below.

Some of the chemical structures which are presented in this specification and the appended claims have been drawn using the convention which employs lines to represent alkyl radicals, which is known by those of skill in the art.

The term "alkyl" as used herein means a saturated hydrocarbon radical having from one to ten carbon atoms, and within which includes from one to five carbon atoms, and further within which includes from one to three carbon atoms, which can be a straight or branched chain. Representative of such radicals are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl and the like.

The term "alkoxy" as used herein means an alkyl radical, as defined above, having one or more hydrogen atoms replaced by an oxygen atom. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "aryl" as used herein means unsubstituted 5- and 6-membered single-ring aromatic radicals, for example, phenyl.

The term "analgesia" as used herein means the reduction, or absence, of sensibility to pain, designating particularly the relief of pain without loss of consciousness.

The term "animal" as used herein includes mammals and nonmammals, and further includes humans and non-human mammals.

The abbreviation "Bu" as used herein means butyl ($-CH_2CH_2CH_2CH_3$).

The term "acyloxy" as used herein means $-O-\overset{O}{\overset{\|}{C}}-R^3$.

The term "composition" as used herein means a product which results from the combining of more than one ingredient.

The abbreviation "DMF" as used herein means dimethylformamide.

The abbreviation "DSC" as used herein means Differential Scanning Calorimetry.

The phrase "EC_{50}" dose as used herein means that dose of a compound or drug which produces a 50% inhibition in a biological effect, such as contractions in isolated segments of guinea pig ileum.

The phrase "ED_{50} dose" as used herein means that dose of a compound or drug which produced a biological effect, such as producing analgesia, in 50% of the animals to which the compound or drug was administered.

The abbreviation "Et" as used herein means ethyl ($-CH_2CH_3$).

The abbreviation "EtOH" as used herein means ethanol (CH_3CH_2OH).

The abbreviation "Et_3N" as used herein means triethylamine.

The abbreviation "EtOAc" as used herein means ethyl acetate.

The term "halogen" as used herein means chlorine (Cl), bromine (Br), fluorine (F) and/or iodine (I).

The term "heteroaryl" as used herein means an aryl radical, as defined above, including from one to four heteroatoms, as defined below. Representative heteroaryls include thienyl, furanyl, pyridinyl, imidazolyl, pyrimidyl, (is)oxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrrolyl and the like.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen.

The term "hydroxy" as used herein means the group -OH.

The abbreviation "HOAc" as used herein means acetic acid.

The term "intragastrically" and/or the abbreviation "i.g." as used herein means that a compound or drug was administered into the stomach.

The abbreviation "Me" as used herein means methyl ($-CH_3$).

The abbreviation "MeOH" as used herein means methanol (CH_3OH).

The abbreviation "MPLC" as used herein means Medium Pressure Liquid Chromatography.

The abbreviation "n-BuOH" as used herein means n-butanol ($CH_3CH_2CH_2CH_2OH$).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, as defined directly

above, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical compound or pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

The phrase "pharmaceutically-acceptable salts" as used herein refers to non-toxic salts of the compounds of the present invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid, or which are prepared by reacting the free acid with a suitable base. Representative salts include the hydrochloride, hydrobromide, sulfate, bisulfate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napsylate, clavulanate and the like salts and

alkali metal salts such as sodium and potassium and alkaline earth salts, such as calcium and magnesium.

The term "phenyl," and the abbreviation "Ph," as used herein means the group C_6H_5-, derived from benzene.

The phrase "protecting group" as used herein means substituents which protect the reactive functional group from undesirable chemical reactions. Examples of such protecting groups include esters of carboxylic acids, ethers of alcohols and acetals and ketals of aldehydes and ketones.

The phrase "N-protecting group" or "N-protected" as used herein means those groups intended to protect the N-terminus of an amino acid or peptide, to protect an amino group against undesirable reactions during synthetic procedures and includes, but is not limited to, sulfonyl, acyl, acetyl, pivaloyl, t-butyloxycarbonyl (Boc), carbonylbenzyloxy (Cbz), benzoyl and an L- or D-aminoacyl residue, which may itself be N-protected similarly.

The abbreviation "s.c." as used herein means that a compound or drug was administered subcutaneously.

The phrase "therapeutically-effective amount" as used herein means an amount of a compound, material, or composition which is an effective dose for eliminating or ameliorating pain in an animal, or for producing some other desired therapeutic effect, at a reasonable benefit/risk ratio applicable to any medical treatment.

The abbreviation "THF" as used herein means tetrahydrofuran.

The phrases "title compound" and "title product" as used herein mean that compound or product whose chemical name is given, and/or whose structure is shown, in the particular example referred to. If no particular example is referred to, it means that compound or product whose chemical name is given, and/or whose structure is shown, in the particular example in which it appears.

(2) Description of Invention

In one aspect, the present invention provides compounds comprising a structure of Formula I, as described above, and pharmaceutically-acceptable salts, esters and amides thereof.

The compounds of the present invention comprise a class of substituted dibenzoxazepine compounds in which the 2-, 3-, 5- and/or 8-position, and/or the side chain, is substituted. Such compounds have been shown to exhibit activity as prostaglandin E_2 antagonists.

Specific compounds within the scope of the invention include, but are not limited to, the compounds discussed in the examples presented below, as well as the pharmaceutically-acceptable salts, esters and amides thereof.

Contemplated equivalents of the compounds described in Formula I include compounds which otherwise correspond thereto, and which have the same general properties thereof, wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound.

Certain compounds of this invention may exist in geometric or stereoisomeric forms. See, for example, the compounds shown and described in Examples 3 and 4 hereinbelow. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

Certain compounds of the present invention may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with

pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, S. M. Berge et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, *66*:1-19 (1977).)

In other cases, the compounds of the invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the

formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, S. M. Berge et al., "Pharmaceutical Salts," supra.)

In another aspect, the present invention provides pharmaceutically-acceptable compositions which comprise a therapeutically-effective amount of one or more of the compounds of Formula I, as described hereinabove, formulated together with one or more pharmaceutically-acceptable carriers. The pharmaceutical compositions of the invention may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal or vaginal administration.

In yet a further aspect, the present invention provides a method for eliminating or ameliorating pain in an animal, and methods for treating central nervous disorders, including convulsions and ischemia, as well as asthma, enuresis, arrhythmia, diarrhea, dysmenorrhea, osteoporosis, urinary incontinence, gastric hypermotility and irritable bowel syndrome in an animal, comprising administering a therapeutically-effective amount of a compound of Formula I, as described hereinabove, to the animal.

The most preferred embodiment of the present invention is the compound described in Example 8 below.

(3) Utility

Compounds of the present invention exhibit activity as prostaglandin E_2 antagonists (prostaglandin antagonists of the E_2 series).

Compounds within the present invention, and the pharmaceutical compositions comprising one or more of these compounds, are useful as analgesic agents for the elimination or amelioration of pain in animals.

In addition to treating pain, these compounds and compositions would be useful in treating convulsions, ischemia and other central nervous system disorders, as well as osteoporosis, dysmenorrhea, asthma, enuresis, arrhythmia, diarrhea, urinary incontinence, gastric hypermotility and irritable bowel syndrome by virtue of their activity as prostaglandin E_2 antagonists. They would also be useful as antipyretic agents by virtue of this activity.

(4) Methods of Preparation

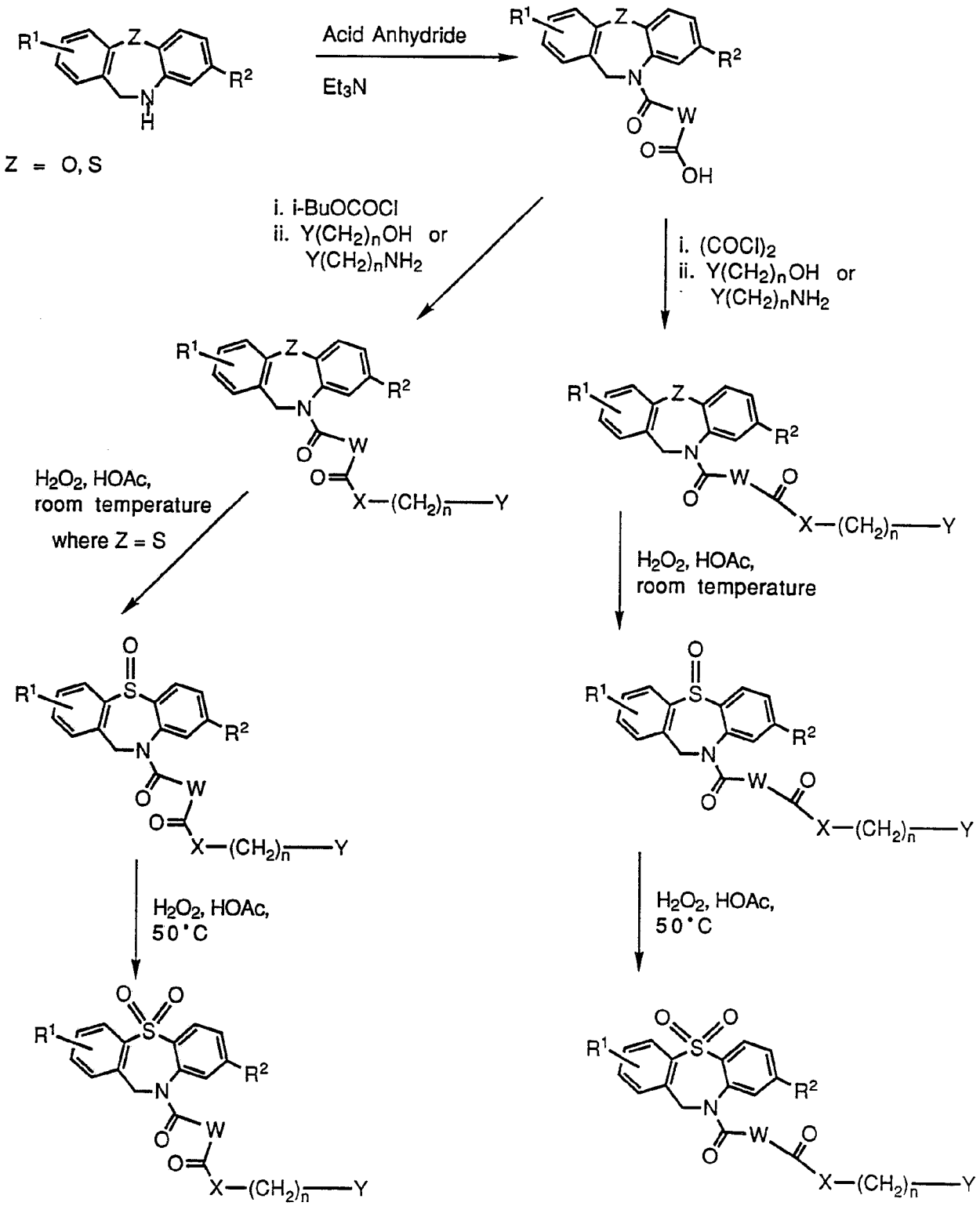
In general, the compounds of the present invention may be prepared by the methods illustrated in the following general reaction schemes, or by modifications thereof, using readily-available starting materials, reagents and conventional synthesis procedures. Unless otherwise specified, the various substituents of the compounds and materials present in the general reaction schemes are defined in the same manner as they are defined above in Formula I.

If a particular enantiomer of a compound of the present invention is desired, it may be prepared by chiral synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

In each of the general reactions schemes, Z may be oxygen, sulfur, -SO- or $-SO_2-$. Where Z is sulfur, oxidation of the sulfur may be achieved with hydrogen peroxide to have Z become -SO-. Oxidation of the -SO- group may then be achieved with hydrogen peroxide to have Z become $-SO_2-$. This is illustrated in General Reaction Scheme No. 1.

In each of the general reaction schemes, W may be -CH=CH-, $-(CH_2)_2-$ or -C≡C- and X may be oxygen or -NH-.

GENERAL REACTION SCHEME NO. 1

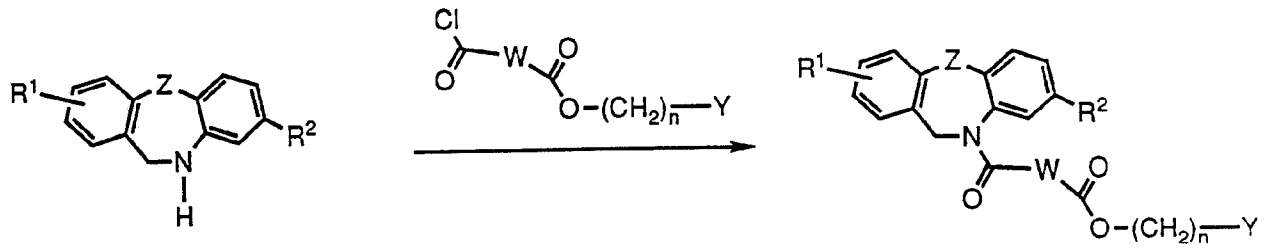


With respect to General Reaction Scheme No. 1, an appropriate heterocycle, such as dibenzoxazepine (where Z is oxygen), mono- or disubstituted with R^1 and/or R^2 wherein R^1 is hydrogen, halogen, or acyloxy and R^2 is hydrogen, halogen, or trifluoromethyl, is reacted with maleic anhydride in the presence of triethylamine.

To yield the saturated or **cis** esters or amides, the resulting acid from above is reacted with i-butyl chloroformate. To the resulting mixed anhydride is added alcohols and amines of general structures, $Y(CH_2)_nOH$ or $Y(CH_2)_nNH_2$ wherein Y can be hydrogen, alkyl, alkoxy, aryl, heteroaryl, amino suitably protected, hydroxy suitably protected, methylamino suitably protected or dimethylamino. If product wherein R^1 is hydroxy is desired, the product is obtained by reacting the acyloxyl intermediate with Na_2CO_3. If product wherein Y is hydroxy, amino, or monomethylamino is desired, the intermediate, wherein Y is protected amino or hydroxy, is reacted with Na_2CO_3.

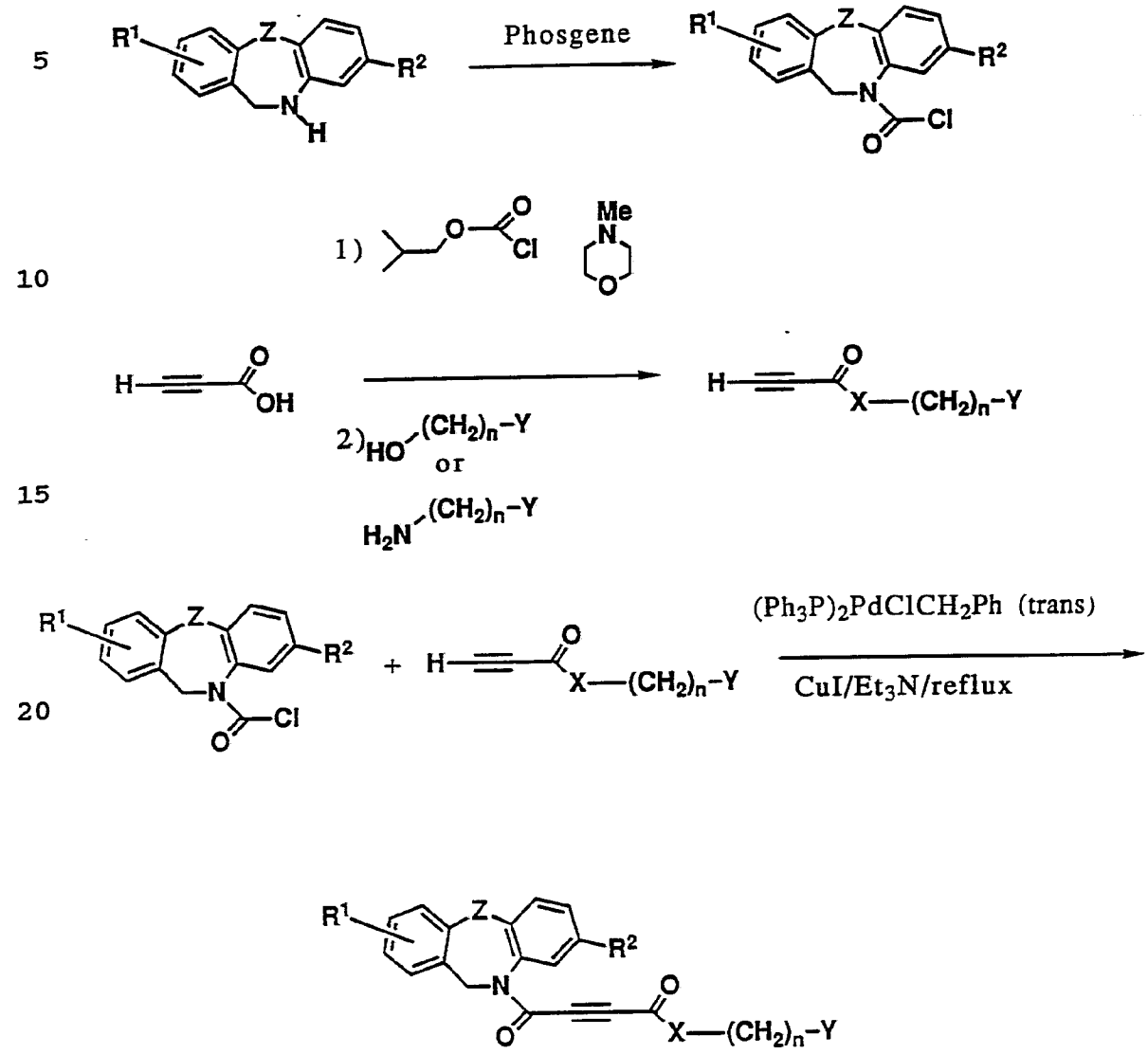
To yield the **trans** esters or amides, the resulting acid from above is reacted with oxalyl chloride. To the resulting acid chloride is added alcohols and amines of general structures, $Y(CH_2)_nOH$ or $Y(CH_2)_nNH_2$ wherein Y can be hydrogen, alkyl, alkoxy, aryl, heteroaryl, amino suitably protected, hydroxy suitably protected, methylamino suitably protected or dimethylamino. If product wherein R^1 is hydroxy is desired, the product is obtained by reacting the acyloxyl intermediate with Na_2CO_3. If product wherein Y is hydroxy, amino, or monomethylamino is desired, the intermediate, wherein Y is protected amino or hydroxy, is reacted with Na_2CO_3.

GENERAL REACTION SCHEME NO. 2



With respect to General Reaction Scheme No. 2, an appropriate heterocycle, such as dibenzoxazepine (where Z is oxygen), mono- or disubstituted with R^1 and/or R^2 wherein R^1 is hydrogen, halogen, or acyloxy and R^2 is hydrogen, halogen, or trifluoromethyl, is reacted with monoesterified fumaric acid chloride wherein the ester group is of the form $Y(CH_2)_nOH$ wherein Y can be hydrogen, alkyl, alkoxy, aryl, heteroaryl, amino suitably protected, hydroxy suitably protected, methylamino suitably protected or dimethylamino. If the product wherein R^1 is hydroxy is desired, the product is obtained by reacting the acyloxyl intermediate with Na_2CO_3. If product wherein Y is hydroxy, amino, or monomethylamino is desired, the intermediate wherein Y is protected amino or hydroxy, is reacted with Na_2CO_3.

GENERAL REACTION SCHEME NO. 3



With respect to General Reaction Scheme No. 3, an appropriate heterocycle, such as dibenzoxazepine (where Z is oxygen), mono- or disubstituted with R^1 and/or R^2 wherein R^1 is hydrogen, halogen, or acyloxy and R^2 is hydrogen, halogen, or trifluoromethyl, is reacted with phosgene in a suitable solvent such as toluene, to give the corresponding carbamoyl chloride.

Propynoic acid is activated, for instance, by means of a mixed anhydride coupling with isobutylchloroformate, and converted to the appropriate amide or ester, in which "X," "Y," and "n" have the same meaning as in General Reaction Scheme No. 1. This acetylenic amide or ester is then reacted with the appropriate dibenzoxazepine carbamoyl chloride in the presence of *trans*-benzyl(chloro)bis(triphenylphosphine)palladium-(II) and cuprous iodide in refluxing triethylamine, to give the desired product.

The conditions for carrying out the individual steps in each of the general reaction schemes presented above are conventional, well-known, and capable of wide variation.

Other methods known in the art can also be used to synthesize the compounds of the present invention.

(5) Dosage and Mode of Administration

The compounds of the present invention, and the pharmaceutical compositions comprising one or more of these compounds in combination with a pharmaceutically-acceptable carrier, are useful in treating pain in animals. A physician or veterinarian of ordinary skill in the art can readily determine whether or not a particular patient is in pain.

The pharmaceutical compositions of the present invention, which will typically comprise one or more of the compounds of Formula I as an active ingredient in admixture with one or more pharmaceutically-acceptable carriers and, optionally, with one or more other compounds, drugs or materials, are employed therapeutically and, thus, would generally be used under the guidance of a physician. The appropriate dosage and form of administration of these compositions will be suitably selected by methods which are consistent with conventional pharmaceutical practices.

The pharmaceutical compositions of the present invention may be specially formulated for oral administration in solid or liquid form, for parenteral injection, and/or for rectal or vaginal administration. They may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually. While the preferred routes of administration are orally and parenterally, the most preferred mode of administration is orally.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage

forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the severity of the pain, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required to alleviate or ameliorate a particular patient's pain. For example, the physician or veterinarian could start doses of the compound of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the present invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, dosage levels in the range of from about

.001 mg to about 10 g, more preferably from about 1 mg to about 1000 mg, of active compound (a compound of Formula I) per kilogram of body weight per day are administered to a mammalian patient. However, the total daily usage of the compounds of Formula I, or the pharmaceutical compositions comprising such compounds, will be determined by an attending physician or veterinarian within the scope of sound medical judgement.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

The pharmaceutical compositions of the present invention comprise a compound of the present invention together with one or more pharmaceutically-acceptable carriers thereof and, optionally, with other therapeutic agents. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl

palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient (compound of Formula I) which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration and all of the other factors described above. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods for preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, with one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient (compound of Formula I) is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills,

the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile, injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed

manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient (compound of Formula I), the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is

solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the invention to the body. Such dosage forms can be made by dissolving, dispersing or otherwise incorporating a compound of the present invention in a proper medium, such as an elastomeric matrix material. Absorption

enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate-controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include

isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

The injectable materials can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or in other sterile injectable mediums just prior to use.

The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately

prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the type described above.

The pharmaceutical compositions of the present invention may also be used in the form of veterinary formulations, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules or pellets for admixture with feed stuffs, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension or, when appropriate, by intramammary injection where a suspension or solution is introduced into the udder of the animal via its teat; (3) topical application, for example, as a cream, ointment or spray applied to the skin; or (4) intravaginally, for example, as a pessary, cream or foam.

While the various aspects of the present invention are described herein with some particularity, those of skill in the art will recognize numerous modifications and variations which remain within the spirit of the invention. These modifications and variations are within the scope of the invention as described and claimed herein.

(6) Examples

The following examples describe and illustrate the methods for the preparation of the compounds of the present invention, as well as other aspects of the present invention, and the results achieved thereby, in further detail. Both an explanation of, and the actual procedures for, the various aspects of the present invention are described where appropriate. These examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those of skill in the art will readily understand that known variations of the conditions and processes of the preparative procedures described in these examples can be used to prepare the compounds of the present invention, and the pharmaceutical compositions comprising such compounds.

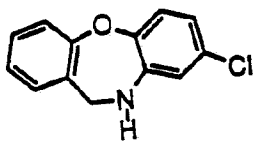
In the examples, all parts are by weight unless otherwise indicated.

All starting materials and equipment employed in the examples are commercially available. Sources for these materials include Sigma Chemical Co. (St. Louis, MO), Aldrich Chemical Co. (Milwaukee, WI), Lancaster Synthesis (Windham, NH), Fisher Scientific (Pittsburgh, PA), Boehringer Mannheim Biochemicals (Indianapolis, IN), Fluka Chemical Corp. (Ronkonkoma, NY) and Chemical Dynamics Corp. (South Plainfield, NJ). Most of the starting materials were obtained from Aldrich Chemical Co. (Milwaukee, WI).

All patents and publications referred to in the examples, and throughout the specification, are hereby incorporated herein by reference, without admission that such is prior art.

Example 1

8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine



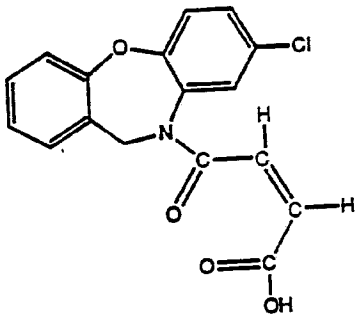
The synthesis of the title compound is described in U.S. Patent No. 3,534,019, which is incorporated herein by reference.

Briefly, 200 parts of 2,5-dichloro-nitrobenzene were heated to 160°C and stirred, and 160 parts of the potassium salt of salicylaldehyde was added over a period of 30 minutes. After the addition was complete, an exothermic reaction took place, and the temperature rose to about 195°C. Heating was discontinued until the reaction subsided, and the mixture was heated for 1 hour at 150°C. The mixture was cooled, ice and water were added, and it was extracted with ether. The ether layer was filtered to remove insoluble material, and the resultant solution was dried over sodium sulfate. The ether solvent was evaporated, and the residual oil was recrystallized from a mixture of hexane and benzene to give 2-(2-nitro-4-chloro-phenoxy)benzaldehyde melting at about 100-101°C.

A solution of 55 parts of the ether obtained in the preceding paragraph in 800 parts of ethanol was hydrogenated over Raney nickel catalyst at room temperature and atmospheric pressure. When hydrogen uptake ceased, the catalyst was removed by filtration, and the ethanol solvent was evaporated. The residue was dissolved in 500 parts by volume of hexane, filtered, and cooled. There was obtained yellowish-white crystals which were separated by filtration to give 8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepine melting at about 94-95°C.

Example 2

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid



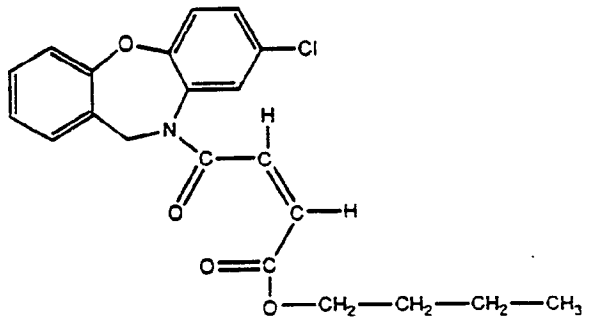
A solution of the title compound of Example 1 (20.0 g, 86.6 mmol) and maleic anhydride (25.5 g, 260 mmol) in CH_2Cl_2 (1 L) and Et_3N (50 mL) was stirred at room temperature for 72 hours under an N_2 atmosphere. The solvent was removed and the resulting residue was suspended in EtOAc (700 mL) and extracted with NaOH (1 M, 3 X 300 mL). The extracts were combined and the pH was brought to 3 with HCl (1 M). The aqueous material was extracted with EtOAc. A precipitate formed at the interface, and was collected by vacuum filtration to yield 7.5 g of a brown solid. The EtOAc was evaporated to yield 7.5 g of a brown solid. The solids were combined and dissolved in isopropyl ether/MeOH, refluxed and decolorized with carbon and filtered through celite. The solvent was evaporated to yield 7.5 g of a yellow solid. The product was then crystallized from isopropyl ether to yield the title compound as a yellow solid (4.5 g).

DSC: 149°C.

Analysis for $C_{17}H_{12}NO_4Cl$:
Calculated: C: 61.92; H: 3.67; N: 4.25.
Found: C: 61.65; H: 3.87; N: 4.31.

Example 3

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate



To a solution of the title compound of Example 2 (500 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) and N-methylmorpholine (0.2 mL, 1.7 mmol) at -60°C under an Argon atmosphere was added isobutylchloroformate (0.2 mL, 1.55 mmol). The reaction solution was stirred at -60°C for 15 minutes and then placed in a ice/MeOH bath (-15°C) for 40 minutes, followed by the addition of n-BuOH (0.3 mL). The reaction mixture was stirred at room temperature for 4 hours.

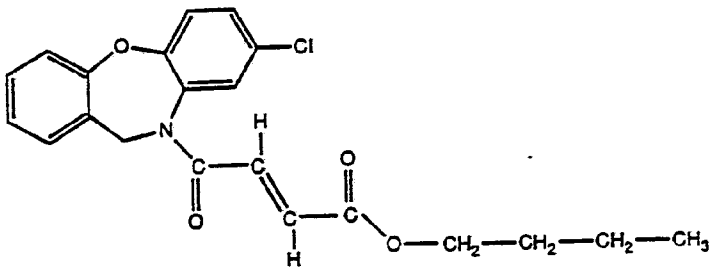
The reaction solution was poured onto EtOAc (200 mL), extracted with HCl (1M, 100 mL), NaOH (1M, 100 mL) and brine (saturated), dried (Na_2SO_4) and evaporated to yield a brown oil. The material was then chromatographed MPLC (silicagel, 3:2 Hexane:EtOAc) to yield the title compound (260 mg) as a colorless oil that crystallized on standing.

DSC: 92°C.

Analysis for $C_{21}H_{20}NO_4Cl$:
Calculated: C: 65.37; H: 5.22; N: 3.63.
Found: C: 65.36; H: 5.39; N: 3.58.

Example 4

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate

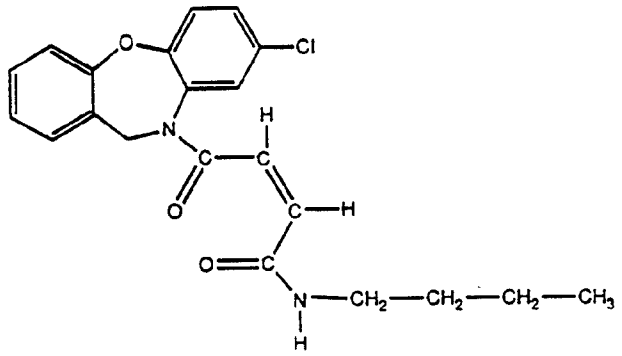


To a solution of the title compound of Example 2 (200 mg, 0.64 mmol) in CH_2Cl_2 (10 mL) and Et_3N (0.2 mL) was added oxalyl chloride (0.2 mL, 1.4 mmol). The solution was stirred at room temperature under a N_2 atmosphere for 1 hour, followed by the addition of n-butanol (5 mL, 55 mmol). The solvent was removed under reduced pressure, and the residue was chromatographed (MPLC, silica gel, 85:15 hexane:EtOAc) to yield the title compound (140 mg) as a colorless oil.

Analysis for $C_{21}H_{20}NO_4Cl$:
Calculated: C: 65.37; H: 5.22; N: 3.63.
Found: C: 65.36; H: 5.39; N: 3.58.

Example 5

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide



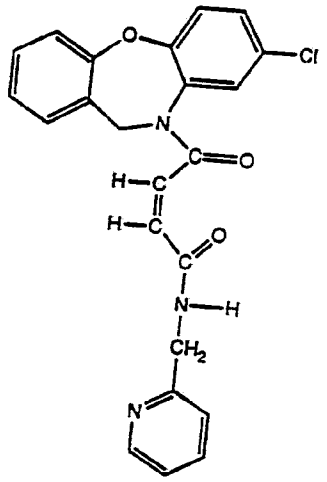
To a solution of the title compound of Example 2 (500 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) and N-methylmorpholine (0.2 mL, 1.7 mmol) at -60°C under an Argon atmosphere was added isobutylchloroformate (0.2 mL, 1.55 mmol). The reaction solution was stirred at -60°C for 15 minutes and then placed in an ice/MeOH bath (-15°C) for 40 minutes, followed by the addition of n-butylamine (0.22 mL, 2.25 mmol). The reaction mixture was stirred at room temperature for 1 hour.

The reaction solution was poured onto $CHCl_3$ (200 mL), extracted with HCl (1M, 100 mL), NaOH (1M, 100 mL) and brine (saturated), dried (Na_2SO_4) and evaporated to yield 500 mg of a yellow oil. The material was then crystallized from ether/hexane to yield the title compound (250 mg) as a white solid.

Analysis for $C_{21}H_{21}N_2O_3Cl$:
Calculated: C: 65.54; H: 5.50; N: 7.28.
Found: C: 64.95; H: 5.58; N: 7.10.

Example 6

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(2-pyridinylmethyl)-2Z-butenamide

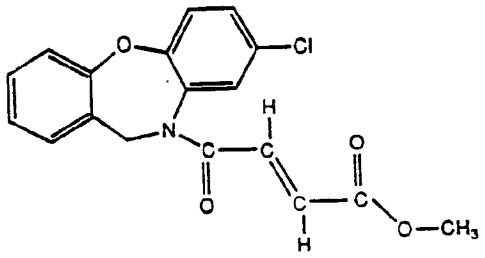


To a solution of the title compound of Example 2 (500 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) and N-methylmorpholine (0.2 mL, 1.7 mmol) at -60°C under an Argon atmosphere was added isobutylchloroformate (0.2 mL, 1.55 mmol). The reaction solution was stirred at -60°C for 15 minutes and then placed in an ice/MeOH bath (-15°C) for 40 minutes, followed by the addition of 2-aminomethyl-pyridine (0.3 mL, 2.5 mmol). The reaction mixture was stirred at room temperature for 4 hours. The solvent was removed and the residue was chromatographed (MPLC, silica gel, 95:5 $CHCl_3$:MeOH) to yield the title compound (475 mg) as a yellow foam.

Analysis for $C_{23}H_{18}N_3O_3Cl \cdot 0.5\ H_2O$:
Calculated: C: 64.41; H: 4.47; N: 9.80.
Found: C: 64.41; H: 4.47; N: 9.55.

Example 7

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate



To a stirring solution of monomethylmaleate (13 g, 100 mmol) in CH_2Cl_2 (150 mL) and Et_3N (25 mL) was slowly added a solution of oxalylchloride (29 mL, 750 mmol) in CH_2Cl_2 (100 mL). The resulting brown solution was stirred for 2 hours, and the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (250 mL) and Et_3N (25 mL). A solution of the title compound of Example 1 (20 g, 100 mmol) in CH_2Cl_2 (125 mL) was added, and the resulting solution was stirred for 16 hours.

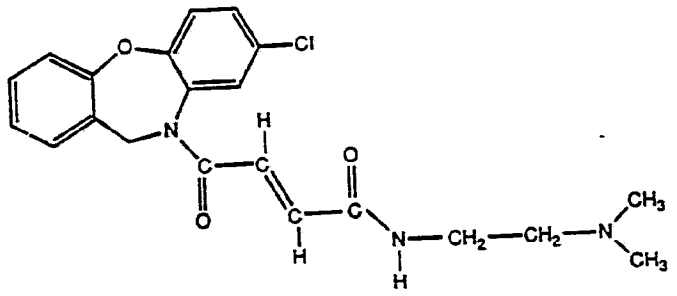
The solvent was removed and the residue was chromatographed on silica gel (CH_2Cl_2) to yield 33 g of a brown gum. The gum was further chromatographed on silica gel (MPLC, 15:85 EtOAc:hexane) to yield the title compound (21 g).

DSC: 125°C.

Analysis for $C_{18}H_{14}NO_4Cl$:
Calculated: C: 62.89; H: 4.10; N: 4.07.
Found: C: 62.79; H: 4.14; N: 4.08.

Example 8

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride

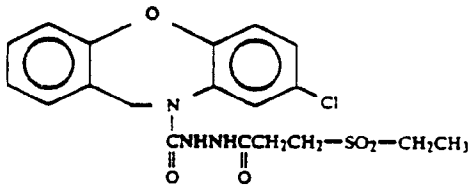


To a solution of the title compound of Example 2 (1 g, 3.2 mmol) in CH_2Cl_2 (50 mL) and Et_3N (1 mL) was added oxalyl chloride (1 mL, 7 mmol). The solution was stirred at room temperature under a N_2 atmosphere for 1 hour. The solvent was removed under reduced pressure, and the residue was redissolved in CH_2Cl_2 (50 mL) and Et_3N (0.5 mL), followed by the addition of N,N-dimethyl-ethylenediamine (803 mg, 9.11 mmol). The reaction mixture was stirred for 2 hours. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (300 mL) and extracted with brine (saturated) and $NaHCO_3$ (saturated) dried (Na_2SO_4) and evaporated to yield 771 mg of the free base. The free base was taken up in EtOH (10 mL) and added to HCl/EtOH (5 mL, 9.5 M). The volume was reduced to 10 mL. The product crystallized on standing at 10°C to yield the title compound (450 mg).

DSC: 211°C.

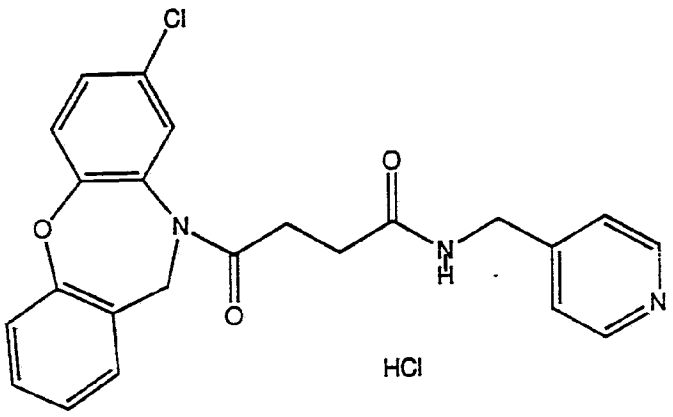
Analysis for $C_{21}H_{22}N_3O_3Cl$ x HCl x .25 H_2O:
Calculated: C: 57.21; H: 5.37; N: 9.53.
Found: C: 57.03; H: 5.52; N: 9.54.

The title compound was determined to have a high water solubility (> 80 mg/mL) by methods known by those of skill in the art. In contrast, 8-chloro-dibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[3(ethylsulfonyl)-1-oxopropyl]hydrazide, the synthesis of which is described in Example 10 of U.S. Patent No. 4,559,336, which is incorporated herein by reference, and whose structure is shown below, has a water solubility of 80 μg/mL.



Example 9

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide



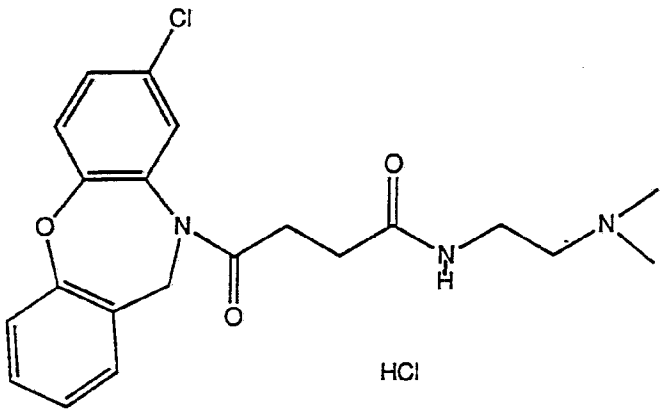
A mixture of 8-chloro-10,11-dihydrodibenz[b,f]-[1,4]oxazepine (5 g), succinic anhydride (5 g), 4-dimethyl-aminopyridine (4 g) and 1,2-dichloroethane (50 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature and shaken successively with 0.7 N HCl, water, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel using a mixture of 1/1 ethyl acetate (EA)/hexane as eluant. Appropriate fractions were pooled and concentrated in vacuo to leave 5.3 g of a thick gum [^{13}C NMR ($CDCl_3$) δ 28.33, 28.69, 48.07]. To a stirred solution of this material (0.87 g) in CH_2Cl_2 (5 mL) at -20°C was added in succession 4-methylmorpholine (0.288 mL) and isobutyl chloroformate (0.34 mL). After 15 minutes, 4-(aminomethyl)pyridine (0.268 mL) was added. The mixture was allowed to warm to room temperature over 16 hours. The mixture was concentrated in vacuo. The residue was extracted with ethyl acetate and water. The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed

over silica gel using a mixture of 10/20/70/1 methanol/ethyl acetate/heptane/triethylamine as eluant. Appropriate fractions were pooled and concentrated to give 0.82 g of the free base of the title compound as a white solid. A solution of this material in CH_2Cl_2 (3 mL) and 7N HCl in dioxane (3 mL) was concentrated in vacuo. The residue was taken up in water (15 mL) and lyophilized to give the title compound as a white solid. [^{13}C NMR (DMSO-d_6) δ 28.5, 29.8, 41.6, 47.3].

Analysis calculated for $C_{23}H_{20}ClN_3O_3$. 0.75 HCl. 0.75 H_2O: C, 59.70; H, 4.85; N, 9.08; Cl, 13.41.
Found: C, 59.80; H, 4.69; N, 9.03; Cl, 13.52.

Example 10

8-chloro-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide



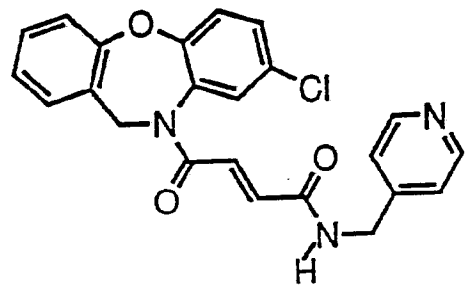
A mixture of 8-chloro-10,11-dihydrodibenz[b,f]-[1,4]oxazepine (5 g), succinic anhydride (5 g), 4-dimethyl-aminopyridine (4 g) and 1,2-dichloroethane (50 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature and shaken successively with 0.7 N HCl, water, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel using a mixture of 1/1 ethyl acetate (EA)/hexane as eluant. Appropriate fractions were pooled and concentrated in vacuo to leave 5.3 g of a thick gum [^{13}C NMR ($CDCl_3$) δ 28.33, 28.69, 48.07]. To a stirred solution of this material (0.87 g) in CH_2Cl_2 (5 mL) at -20°C was added in succession 4-methylmorpholine (0.288 mL) and isobutyl chloroformate (0.34 mL). After 15 minutes, N,N-dimethylethylenediamine (0.29 mL) was added. The mixture was allowed to warm to room temperature over 16 hours. The mixture was concentrated in vacuo. The residue was extracted with ethyl acetate and water. The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed

over silica gel using a mixture of 10/20/70/1 methanol/ethyl acetate/heptane/triethylamine as eluant. Appropriate fractions were pooled and concentrated to give 0.84 g of the free base of the title compound as a white solid. A solution of this material in CH_2Cl_2 (3 mL) and 7N HCl in dioxane (3 mL) was concentrated in vacuo. The residue was taken up in water (15 mL) and lyophilized to give the title compound as a white solid. [^{13}C NMR (DMSO-d_6) δ 28.5, 30.0, 33.8, 42.2, 47.3, 55.7].

Analysis calculated for $C_{21}H_{24}ClN_3O_3.HCl$:
C, 57.54; H, 5.75; N, 9.59; Cl, 16.18.
Found: C, 57.21; H, 5.79; N, 9.50; Cl, 16.09.

Example 11

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide



To a stirring solution of the title compound of Example 7 (1.0 g) in THF (30 mL) and H_2O (15 mL) was added lithium hydroxide (210 mg). The resulting solution was stirred for 2 hours. The solvent was removed under reduced pressure and EtOAc (300 mL) and HCl (1M, 100 mL) were added to the residue. The EtOAc was separated, dried (Na_2SO_4) and evaporated to yield 973 mg of a solid, which was used in the manner described in the next paragraph without further purification.

To a stirring solution of the product synthesized in the preceding paragraph (930 mg) and 4-aminomethyl pyridine (305 mg) in DMF (20 mL) at 0°C under a nitrogen atmosphere was added triethylamine (285 mg), 1-hydroxybenzotriazole hydrate (381 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (541 mg). The reaction mixture was then stirred at ambient temperature for 18 hours. The solvent was

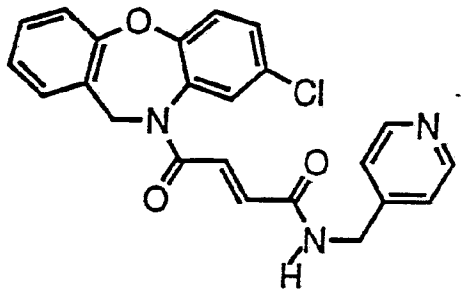
removed, and to the residue was added HCl (1 M, 200 mL), followed by extraction with EtOAc (3 x 200 mL). NaOH (1 M, 200 mL) was added to the aqueous portion, which was extracted with EtOAc (3 x 200 mL), dried (Na_2SO_4) and evaporated to yield an oil. This oil was crystallized from ether/hexane to yield the title compound (780 mg) as a white solid.

DSC 238.7°C.

Analysis for $C_{23}H_{18}N_3O_3Cl$:
Calculated C: 65.80; H: 4.32; N: 10.01; Cl: 8.44.
Found: C: 65.51; H: 4.36; N: 10.05; Cl: 8.17.

Example 12

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride



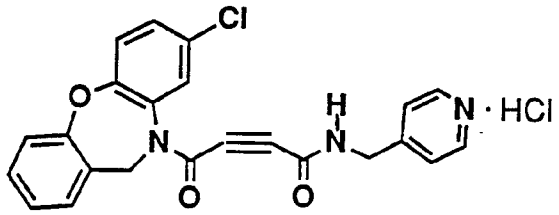
HCl

The free base of the title compound of Example 11 was dissolved in HCl (1M, 40 mL) and lyophilized. The product was then dissolved in glacial acetic acid (20 mL) and lyophilized to yield 638 mg of the hydrochloride salt of the title Compound of Example 11.

Analysis for $C_{23}H_{18}N_3O_3Cl$ x 0.9 HCl x 1 H_2O:
Calculated: C: 58.69; H: 4.48; N: 8.93; Cl: 14.31.
Found: C: 58.39; H: 4.14; N: 8.93; Cl: 13.94.

Example 13

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2-butynamide, monohydrochloride



8-Chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carbonyl chloride is synthesized in the manner described in U.S. Patent No. 3,534,019: Phosgene (13 g, 131.4 mmol) in toluene (45 g) is stirred for 2 hours at 5-10°C, and then diethyl ether (70 g) is added. This is followed by the addition of a solution of 8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine (18.9 g, 81.6 mmol), prepared in the manner described in Example 1, and triethylamine (7.2 g, 9.92 mL, 71.2 mmol) in diethyl ether (140 g). After the addition is complete, the mixture is stirred for 2 hours, and then is filtered. The solvent is then evaporated from the filtrate, and the resulting residue is recrystallized from hexane, giving 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carbonyl chloride.

A 1 L round bottom, three-necked flask is fitted with a magnetic stirrer, N_2 inlet, stopper, and Y-tube which contains a thermometer and a drying tube outlet. Propiolic acid (5.0 g, 4.39 mL, 71.4 mmol) is charged into the flask, as is methylene chloride (300 mL) and

N,N-dimethylformamide (100 mL), and 5A molecular sieves (20 g). The N_2 is turned on and the mixture is cooled to -40°. N-methylmorpholine (8.30 g, 9.02 mL, 82.08 mmol) is added, and the mixture is stirred at a low temperature for 40 minutes. The temperature is lowered to -60°, and isobutylchloroformate (10.24 g, 9.81 mL, 74.97 mmol) is added all at once. The mixture is warmed to -15° and stirred at that temperature for 1 hour. The mixture is then recooled to -60°, and 4-(aminomethyl)pyridine (8.49 g, 7.97 mL, 78.52 mmol) is added all at once. The mixture is allowed to stir at room temperature overnight. The mixture is then filtered through a sintered glass funnel, and the residue is washed with methylene chloride. The filtrate and washes are combined and washed with aqueous phosphate buffer at pH 7.5. The organic phase is dried ($MgSO_4$), filtered, and stripped to a solid, which is subjected to silica column chromatography. The resulting N-[(4-pyridyl)methyl]propynamide is used directly in the next step.

8-Chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carbonyl chloride (2.0 g, 6.8 mmol), N-[(4-pyridyl)methyl]-propynamide (1.09 g, 6.8 mmol), cuprous iodide (0.10 g, 0.52 mmol), *trans*-benzyl(chloro)bis(triphenyl-phosphine)palladium(II) (0.10 g, 0.26 mmol), and triethylamine (40 mL) are charged into a 100 mL flask, and refluxed under argon for 16 hours. The mixture is stripped to a solid, and partitioned between methylene chloride and aqueous phosphate buffer pH 7.5. The organic phase is dried ($MgSO_4$), filtered, and stripped to a solid. The solid is subjected to silica column chromatography to yield the free base of the title compound.

The resulting free base is dissolved in diethyl ether. The solution is treated with 5 mL of 6 N HCl/dioxane. The resulting precipitate is collected by filtration and is dried to give the title compound.

The foregoing examples are provided to enable one of ordinary skill in the art to practice the present invention. These examples are merely illustrative, however, and should not be read as limiting the scope of the invention as it is claimed in the appended claims.

(7) Description of Assays

(a) Writhing Assay

The Writhing Assay is one of the most widely-used experimental procedures for measuring the analgesic activity of different narcotic and nonnarcotic analgesic agents, and involves the continuous, chemically-induced pain of visceral origin to an animal, such as a mouse or rat. [Gyires et al., *Arch. int. Pharmacodyn, 267,* 131-140 (1984); C. Vander Wende et al., *Fed. Proc., 15,* 494 (1956); Koster et al., *Fed. Proc., 18,* 412 (1959); and Witken et al., *J. Pharmacol. exp. Ther., 133,* 400-408 (1961).] Chemicals which may be used to induce this pain include phenylbenzoquinone (PBQ) and acetic acid. As a result of the chemical irritation to the animal, a characteristic stretching and writhing of the animal (dorsiflexion of the animal's back, extension of its hindlimbs and the strong contraction of its abdominal musculature) will generally occur. The intensity of this pain reaction is determined by the number of writhes exhibited by the animal during a given period of time. Drugs which reduce the number of writhes of the animal appear to restore the normal nociceptive threshold of the animal.

Compounds of the present invention exhibit analgesic activity in mice, as shown by the results of the Writhing Assay presented in Table I hereinbelow.

Charles River male albino mice, weighing 20 to 30 grams, were used in this assay.

Thirty minutes after subcutaneous or intragastric administration to ten mice of 30 mg per kilogram of body weight of a compound of the present invention ("test compound"), 0.1 mg per 10 g of body weight of a 0.025% w/v solution of PBQ was injected intraperitoneally into each mouse. Ten mice which were given saline in place of a test compound of the invention were used as a control group.

Five minutes later, each mouse was individually placed into a glass beaker for observation, and the number of writhes occurring during the following ten-minute period was counted.

A test compound was considered to have produced analgesia in a mouse if, in accordance with the conditions set forth above, and under the test criteria employed for this assay, after the administration of 30 mg per kilogram of body weight of a compound of the present invention to the mouse, the number of writhes elicited by a mouse injected with PBQ was equal to, or less than, one-half the median number of writhes recorded for the saline-treated control group of mice that day, as described by Taber in "Predictive Value of Analgesic Assays in Mice and Rats," *Advances in Biochemical Psychopharmacology*, *8*, 191 (**1974**).

The results for the particular compounds of the present invention analyzed in this assay, and discussed in the examples identified below which correspond thereto, are presented in Table I hereinbelow as fractions under the heading "WRITHING ASSAY." The fractions indicate the number of mice, out of ten, in which the test compound produced analgesia.

The standard initial screening dose of a test compound employed in this assay was 30 mpk per gram of body weight for both routes of administration. If this initial screening dose of the test compound produced analgesia in seven of ten mice, then the effect of additional doses of the test compound on the writhing response was evaluated, and then the ED_{50} dose was generally calculated. (The slopes of the dose-response curves for all test compounds analyzed were compared as described by Tallarida and Murray, Manual of Pharmacologic Calculations, Page 11 (Springer Verlag, New York, 1981)).

All ED_{50} doses calculated are also presented below as whole numbers in Table I under the heading "WRITHING ASSAY." As Table I shows, the most potent compound of the present invention tested in the Writhing Assay was the compound shown and discussed in Example 8. Thus, 4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride (Example 8) was determined to be the most potent compound of the invention tested in this assay and, thus, is the most preferred compound of the present invention.

(b) Prostaglandin (PGE) Antagonism Assay

In order to determine the effectiveness of several of the compounds of the present invention ("test compounds") as prostaglandin E_2 antagonists, a prostaglandin antagonism assay was conducted, as described below, to determine the ability of these compounds to inhibit prostaglandin E_2-induced contractions of segments of guinea pig ileum. If a test compound inhibits prostaglandin E_2-induced contractions, it suggests that the compound functionally antagonizes prostaglandin E_2.

Male albino guinea pigs weighing 200 to 500 grams were sacrificed by cervical dislocation. The ilea were then quickly removed from the guinea pigs and placed in a modified Tyrode solution, a solution which is known to those skilled in the art, containing one-half of the usual amount of magnesium ions.

Segments of ileum about 2 cm long were then cut and mounted in a 10 mL tissue bath containing the modified Tyrode solution. The solution was maintained at 37°C and aerated with a gaseous mixture of 95% oxygen and 5% carbon dioxide. Data for a control prostaglandin E_2 dose response curve plotting concentration of prostaglandin E_2 versus the intensity of contractions, detected isotonically, was then obtained by experimentally adjusting the dose of the prostaglandin E_2 being injected into the tissue bath, in a manner known by those of skill in the art.

Solutions or suspensions containing an initial concentration (3 micromolar) of a test compound in modified Tyrode solution ("test solutions / suspensions") were then separately substituted for the control bath solution. Each test solution / suspension was then kept in constant contact with the ileum tissue, except for brief periods to drain the bath in preparation for rinsing with fresh test solution / suspension. A second prostaglandin E_2 dose response

curve was then generated for prostaglandin E_2 in the presence of a test compound.

A dose ratio of EC_{50} doses was then calculated from the results of each test in a manner known by those of skill in the art. A test compound was determined to be "active" if the initial concentration used yielded at least a two-fold shift (dose ratio greater than or equal to 2) in the dose response curve for prostaglandin E_2. An estimated pA_2 value (a statistical constant which is a common measure of expressing the potency of a particular drug as an antagonist) was reported for "active" compounds under the assumption that the slope of the Schild plot does not deviate significantly from -1.0. If the initial concentration of test compound yielded at least a five-fold shift (dose ratio greater than or equal to 5) in the dose response curve for prostaglandin E_2, then varying concentrations of the test compound were assayed, and a PA_2 value for that compound was calculated by Schild plot calculations, as described by H. O. Schild, "pA, A New Scale for the Measurement of Drug Antagonism," Br. J. Pharmacol, 2, 189 (1947). The higher the value calculated for the PA_2, the more potent a particular compound is as a prostaglandin E_2 antagonist.

The results of this prostaglandin antagonism assay are also presented in Table I below. The compounds of the present invention which were tested in this assay, and for which results are presented in Table I, correspond to the particular examples specified in Table I.

Table I

Data Generated from the Assays

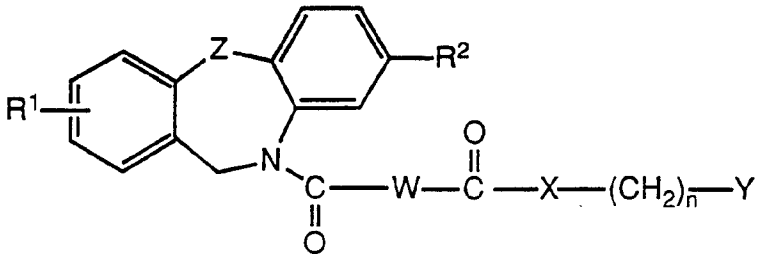
Example Number	WRITHING ASSAY Number out of Nine or Ten or ED_{50} Dose (mpk)		PGE IN GUINEA PIG ILEUM
	S.C.	I.G.	pA_2
2	4/10	1/10	*
3	4/10	6/10	*
4	6/10	6/10	*
5	6/10	4/10	*
7	6/9	3/10	*
8	8.3	8.3	5.73
9	*	6/10	5.62
10	*	6/9	*

* = Not Tested.

While the present invention has been described herein with some specificity, and with reference to certain preferred embodiments thereof, those of ordinary skill in the art will recognize numerous variations, modifications and substitutions of that which has been described which can be made, and which are within the scope and spirit of the invention. For example, effective dosages other than the preferred ranges set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the animal being treated, dosage-related adverse effects, if any, and analogous considerations. Likewise, the specific pharmacological responses observed may vary according to, and depending upon, the particular active compound selected, or whether there are present certain pharmaceutical carriers, as well as the type of formulation and mode of administration employed. Such expected variations and/or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended therefore that all of these modifications and variations be within the scope of the present invention as described and claimed herein, and that the invention be limited only by the scope of the claims which follow, and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound having a structure of the formula:



or a pharmaceutically-acceptable salt, ester or amide thereof, wherein:

R^1 is hydrogen, halogen, hydroxy or $-O-\overset{O}{\overset{\|}{C}}-R^3$;

R^2 is hydrogen, halogen or trifluoromethyl;

R^3 is hydrogen or alkyl;

W is -CH=CH-, $-(CH_2)_2-$ or -C≡C-;

X is oxygen or -NH-;

n is an integer of from 0 to 5;

Z is oxygen, sulfur, $-\overset{O}{\overset{\|}{S}}-$ or $-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-$

Y is hydrogen, alkyl, hydroxy, alkoxy, aryl,

heteroaryl, $-NH_2$, $-\overset{H}{\underset{|}{N}}-CH_3$, or $-\overset{CH_3}{\underset{|}{N}}-CH_3$,

with the proviso that Y is not hydroxy, alkoxy,

$-NH_2$, $-\overset{H}{\underset{|}{N}}-CH_3$ or $-\overset{CH_3}{\underset{|}{N}}-CH_3$ when n is 0.

2. A compound of Claim 1 wherein R^1 and R^2 are each independently hydrogen or halogen.

3. A compound of Claim 2 wherein R^1 is hydrogen and R^2 is halogen.

4. A compound of Claim 3 wherein R^2 is chlorine.

5. A compound of Claim 4 wherein n is an integer of from 0 to 3.

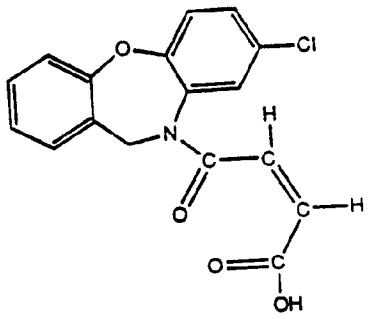
6. A compound of Claim 5 wherein Y is alkyl, hydroxy, alkoxy, aryl, heteroaryl, $-NH_2$, $-\overset{H}{\underset{|}{N}}-CH_3$ or $-\overset{CH_3}{\underset{|}{N}}-CH_3$.

7. A compound of Claim 6 wherein Y is methyl, ethyl, propyl, hydroxy, methoxy, ethoxy, phenyl, thiophene, furan, pyridine or $-\overset{CH_3}{\underset{|}{N}}-CH_3$ and Z is oxygen.

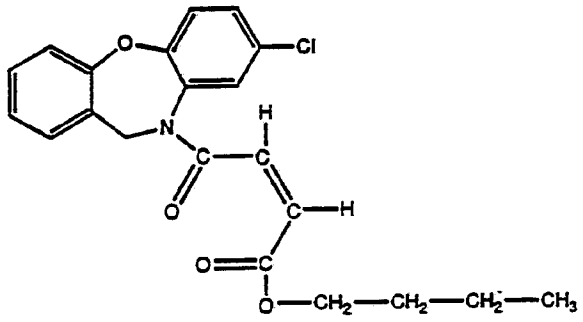
8. A compound of Claim 7 wherein Y is methyl, ethyl, propyl, hydroxy, methoxy, pyridine or $-\overset{CH_3}{\underset{|}{N}}-CH_3$.

9. A compound of Claim 8 wherein Y is methyl, hydroxy, pyridine or $-\overset{CH_3}{\underset{|}{N}}-CH_3$.

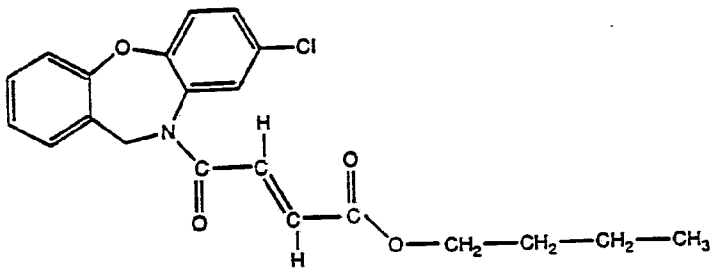
10. A compound of Claim 1, wherein the compound is:



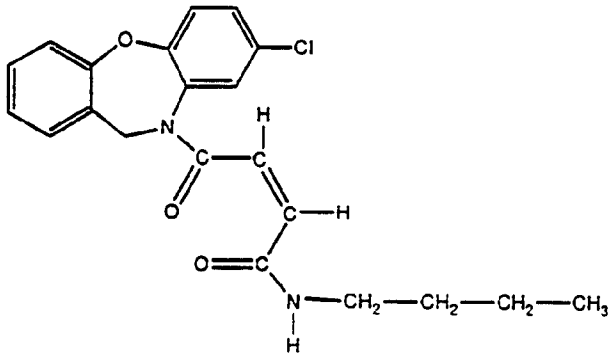
11. A compound of Claim 1, wherein the compound is:



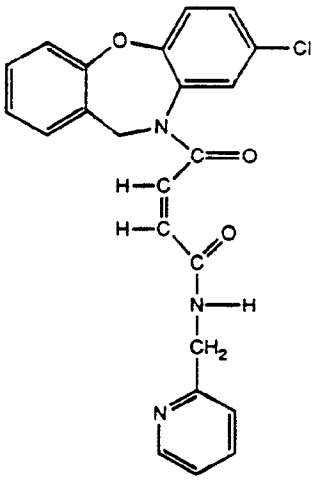
12. A compound of Claim 1, wherein the compound is:



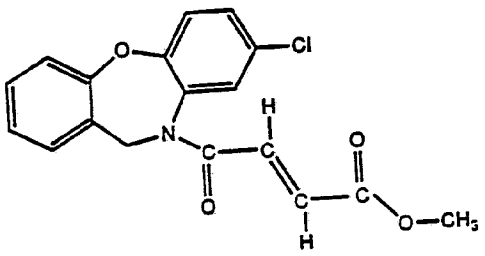
13. A compound of Claim 1, wherein the compound is:



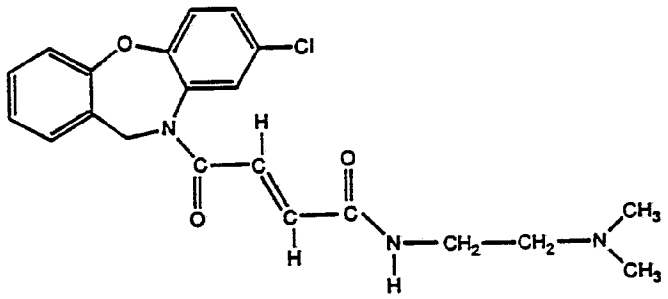
14. A compound of Claim 1, wherein the compound is:



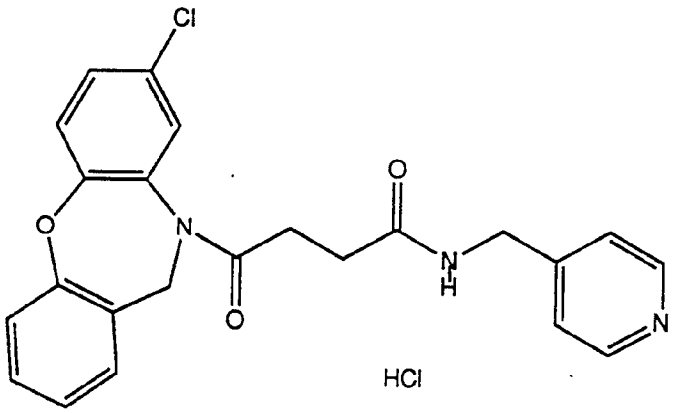
15. A compound of Claim 1, wherein the compound is:



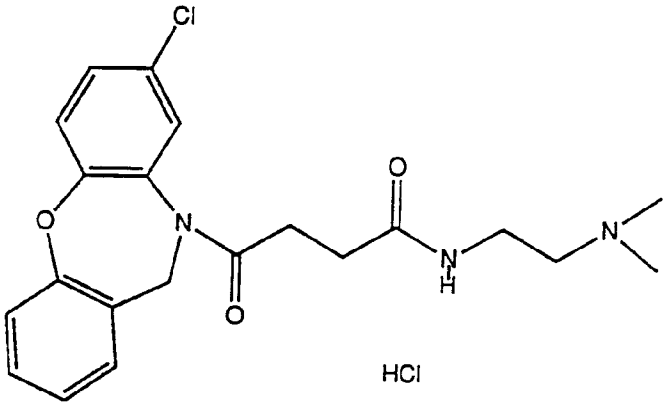
16. A compound of Claim 1, wherein the compound is:



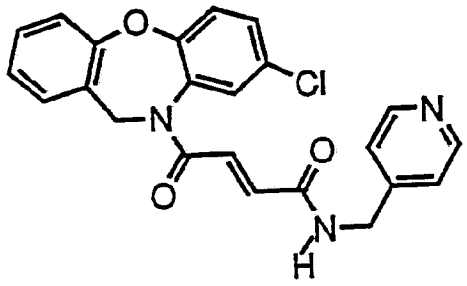
17. A compound of Claim 1, wherein the compound is:



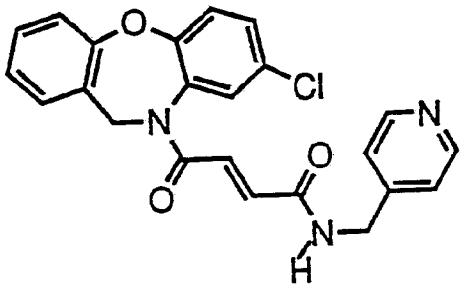
18. A compound of Claim 1, wherein the compound is:



19. A compound of Claim 1, wherein the compound is:



20. A compound of Claim 1, wherein the compound is:



HCl

21. A compound of Claim 1 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(2-pyridinylmethyl)-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

22. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically-effective amount of a compound of Claim 1.

23. The pharmaceutical composition of Claim 22 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

24. A method for treating central nervous disorders in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

25. The method of Claim 24 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride.

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

26. A method for treating pain in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

27. The method of Claim 26 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

28. A method for treating asthma in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

29. The method of Claim 28 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

30. A method for treating enuresis in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

31. The method of Claim 30 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

32. A method for treating arrhythmia in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

33. The method of Claim 32 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

34. A method for treating diarrhea in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

35. The method of Claim 34 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

36. A method for treating dysmenorrhea in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

37. The method of Claim 36 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

38. A method for treating osteoporosis in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

39. The method of Claim 38 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

40. A method for treating convulsions in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

41. The method of Claim 40 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

42. A method for treating ischemia in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

43. The method of Claim 42 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

44. A method for treating urinary incontinence in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

45. The method of Claim 44 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

46. A method for treating gastric hypermotility in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

47. The method of Claim 46 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

48. A method for treating irritable bowel syndrome in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

49. The method of Claim 48 wherein the compound is:

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butanoic acid;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenoate;

Butyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

N-butyl-4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2Z-butenamide;

Methyl 4-(8-chloro-10,11-dihydrodibenz[b,f]-oxazepin-10-yl)-4-oxo-2E-butenoate;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-N-[2-(dimethylamino)ethyl]-4-oxo-2E-butenamide, monohydrochloride;

8-chloro-γ-oxo-N-(4-pyridinylmethyl)dibenz[b,f]-[1,4]oxazepine-10(11)-butanamide;

8-chloro-N-oxo-N-[2-(dimethylamino)ethyl]-γ-oxodibenz-[b,f][1,4]oxazepine-10(11)-butanamide;

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide; or

4-(8-chloro-10,11-dihydrodibenz[b,f]oxazepin-10-yl)-4-oxo-N-(4-pyridinylmethyl)-2E-butenamide, monohydrochloride.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/08103

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D267/20; C07D413/12; A61K31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,4 559 336 (R.A. MUELLER) 17 December 1985 cited in the application see the whole document	1,22
A	EP,A,0 012 385 (CHUGAI SEIYAKU KABUSHIKI KAISHA) 25 June 1980 cited in the application see the whole document	1,22

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 NOVEMBER 1992	02.17.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALLARD M.S.

INTERNATIONAL SEARCH REPORT

I national application No.

PCT/US92/08103

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 24-49 are directed to a method of treatment of the human/ animal body, the search has been carried out and based on the alleged effects of the compounds/compositions

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9208103 SA 65242

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/11/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4559336	17-12-85	AU-B- 576944	08-09-88
		AU-A- 5400986	28-08-86
		CA-A- 1251204	14-03-89
		EP-A,B 0193822	10-09-86
		JP-A- 61210078	18-09-86
		US-A- 4614617	30-09-86
EP-A-0012385	25-06-80	JP-A- 55076869	10-06-80
		AT-T- 2522	15-03-83
		CA-A- 1132545	28-09-82
		US-A- 4290953	22-09-81